UNIT-IV Micromeritics

Micromeritics involve the study of the science and technology of small particles, and of the order of micrometer size.

micro + meritics
↓ ↓
Particle-size measure

⇒ It involves the study of
↓
fundamental and derived properties of
↓
individual as well as collection of particles.

★ 1 μm = 10^{-3} mm or 10^{-6} m.

Applications:

1. **Release and dissolution** - Particle size and surface area influence the release of drug from a dosage form that is administered orally, rectally, parenterally and topically.

Surface Area ∝ dissolution & release

2. **Absorption and drug action** - Particle size and surface area influence the drug absorption and subsequently the therapeutic action.

Surface Area ↑ ∝ dissolution ↑ ∝ absorption ↑ ∝ drug action ↑

3. **Physical Stability** :- Particle size influence the physical stability of suspension and emulsions.

Smaller the size of particle, better of the physical stability. Optimum particle size is essential for physical stability.

4. **Dose uniformity** - Good flow properties of granules and powders are important in manufacture of tablets and capsules.

- The distribution of particles should be uniform in terms of its number and weight.

Particles - Characteristics

According to USP, particle is defined as the smallest discrete unit.

Proper [size, shape] influence the dissolution rate, absorption rate, taste, colour, stability etc.

⇒ Particle size :-

A particle size is expressed by radius or diameter.

- If all the particles have same diameter
  ↓
  powder sample is called as monodisperse.
- Most pharmaceutical powders are not of equal size
  ↓
  So are polydisperse.

⇒ Particle size is generally expressed in micrometer or micron (μ).

⇒ Large particles can be expressed in millimeters (mm).

1 mm = 10^{-3} m
1 μm = 10^{-6} m
1 hm = 10^{-9} m
(pico m) 1 pi = 10^{-12} m
1 Å = 10^{-10} m

⇒ If the shape of a particle is perfectly spherical → it is easy to express it by diameter.

⇒ But when particle is not spherical or non spherical, then it is difficult to express in diameter.

⇒ In case of Non-spherical particles
↓
measurement is based on hypothetical sphere which is referred as equivalent spherical diameter of particles. →

① Surface diameter: (D_s):-

The diameter of a shere having same surface area as particle is called surface diameter.
It is expressed as-

$$D_s = \sqrt{\frac{S}{\pi}}$$

where, S is particle surface area.

② Volume diameter, (D_v):-

The diameter of a sphere having the same volume as the particle is called volume diameter.
It is expressed as -

$$D_v = \left(\frac{6V}{\pi}\right)^{1/3}$$

Where, V is particle volume.

③ Projected diameter, (D_p):-

The diameter of a sphere having the same observed area when the particle viewed normal to its most stable plain.
- It is determined by microscopic technique.

④ Stokes diameter, (D_{ST}):-

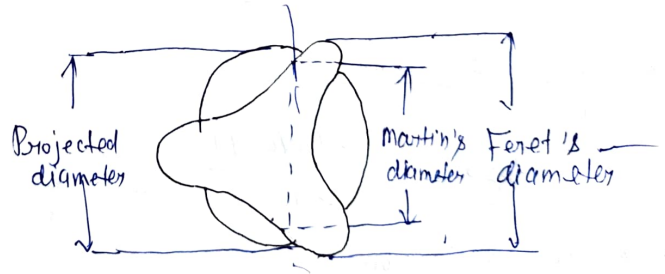
It is diameter of an equivalent sphere undergoes sedimentation at same rate as particle.
- It is measured by sedimentation method.

⑤ Ferret diameter:-

It is the distance between two tangents on opposite sides of the particles parallel to same fixed direction.

⑥ Martin diameter:-

Martin's diameter is the length of the line that bisects the particle image.
⇒ A line may be drawn in any direction, but must be drawn in the same direction for other particles also.



Particle size distribution

⇒ A powder of equivalent spheres or spheres with uniform diameter, Its characteristics can be described by a single diameter or equivalent diameter.

⇒ most powders contains particles with a large number of different equivalent diameters.

⇒ The particles size distribution of a powder, or granular material or particles dispersed in the fluid is a list of values or a mathematical function that defines the relative amounts of particles present classified by size.

Average particle size :-

$$\text{Average particle size } (\bar{D}n) = \frac{\Sigma (nxd)}{\Sigma n}$$

Eg.

Size Range	n	d	nxd
1 um - 2 um	2	1	2
3um - 4um	5	2	10
5 um 6um	3	1	3

$\Sigma n = 10$ $\quad$ $\Sigma nd = 15$

Some Significant diameter-

→ Geometric Mean

$$\log \bar{D}geo = \frac{\Sigma (n \log d)}{\Sigma n}$$

→ log normal distribution
→ more appropriate.

→ Arithmatic mean diameter-

$$\bar{D}av = \frac{\Sigma (nd)}{\Sigma n}$$

→ Surface - number mean diameter ($\bar{D}s$)

$$\bar{D}s = \sqrt{\frac{\Sigma nd^2}{\Sigma n}}.$$

→ Volume - surface mean diameter ($\bar{D}vs$)

$$\bar{D}vs = \frac{\Sigma nd^3}{\Sigma nd^2}$$

→ Volume weighted mean diameter ($\bar{D}w$)

$$\bar{D}w = \frac{\Sigma nd^4}{\Sigma nd^3}.$$

Number and Weight Distribution:

⇒ Data collected by → counting technique such as optical microscopy
⇓
based on number distribution.

⇒ Data collected by → sieve analysis, Andreason pipette sedimentation technique
⇓
based on weight distribution.

⇒ It is possible to convert → number distribution
⇓
weight distribution

⇒ Two approaches are generally followed -

① An estimation of the weight distribution can be obtained by → calculation based on the value of nd^3.

(ii) Use of Hatch-Choate equations -

Provided the distribution is log-normal.

It is possible to convert number distribution to weight distribution.

$$\log d_{av} = \log d_{geo} + 1.151 \log^2 \sigma_g$$

Number distribution

$$\log d_{av} = \log d'_{geo} - 5.757 \log^2 \sigma_g$$

weight distribution.

Geometric standard deviation σ_g.

$$\sigma_g = \frac{84\% \text{ undersize or } 16\% \text{ oversize}}{50\% \text{ size}}$$

$$\sigma_g = \frac{50\% \text{ size}}{16\% \text{ undersize or } 84\% \text{ oversize}}$$

Particle Number

⇒ Particle number N is defined as

↓

the number of particles per unit weight of a powder.

Assuming that are spheres,

Volume of a single particle is $= \frac{\pi d_{vn}^3}{6}$.

mass of a single particle is = volume × density

Mass of a single particle $= \frac{\pi d_{vn}^3 \rho}{6}$.

Where d_{vn} = Volume-number mean diameter

ρ = density of particle.

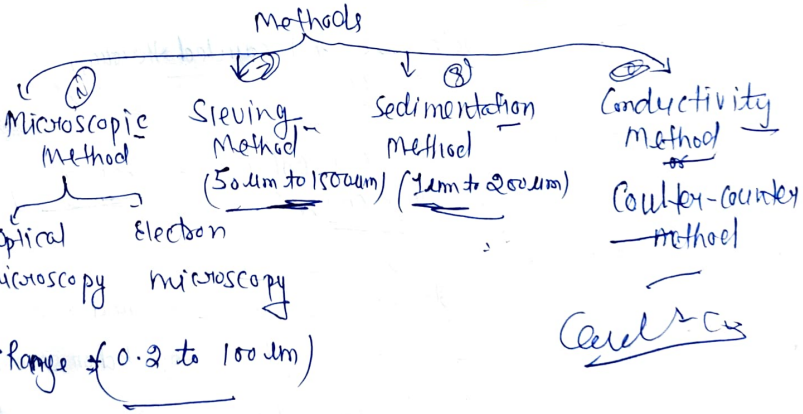
⇒ So number of particles per gram can be obtained by -

$$N = \frac{1 \text{ gm of the powder}}{\text{mass of one particle}}$$

$$N = \frac{1}{\pi d_{vn}^3 \rho / 6} \Rightarrow \boxed{N = \frac{6}{\pi d_{vn}^3 \rho}}$$

Particle Size Determination

- Methods generally used to determine → particle size and particle size distribution



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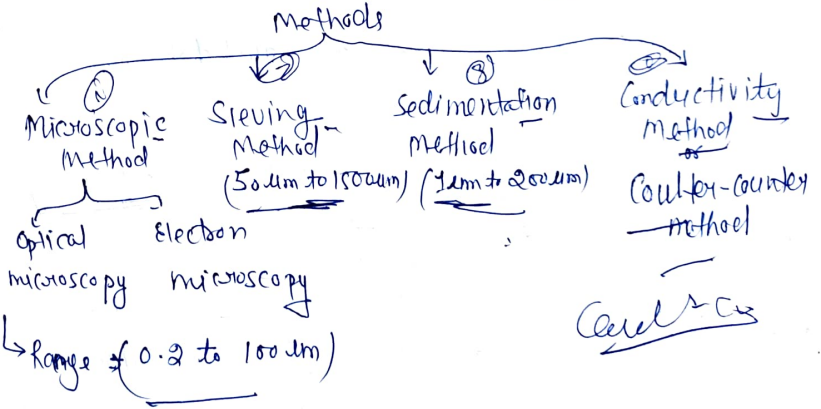


① Microscopic Method :-

- Optical microscopy → generally used for particle size measurement
  ↓
  in the range of 0.2 μm to 100 μm.
- At least 300 to 500 particles must be counted for good size distribution analysis.

Method :-

A dilute suspension of powder is prepared in a liquid vehicle in which it is insoluble.
(If slightly soluble → a saturated solution of powder is used)
⇓
a drop of suspension is mounted on slide
⇓
Observed under the microscope
(eyepiece is fitted with micrometer)
⇓
estimate the particle size and counted through eye piece
⇓
Data scientifically represented as size & frequency distribution curve.

from the data → average particle size and
→ size distribution is determined.

- for ease in counting → field viewed is projected on screen
  or
  ↳ photographed for latter measurment.

- For very small particle → electron microscope or
  → scanning electron microscope may be used.

Advantage

→ Any contamination in the powder can be detected.
→ microscopy allows the observer to view the particles.

Disadvantage

→ diameter is obtained from only two diamensions
  i.e → length and breadth
  → depth of the particle is not measureable.
→ Slow and boring method.

② Sieving Method :-

- Sieving method is an ordinary and simple method.
→ In this method a series of standard sieves are used → placed on a mechanical shaker
  (Sieve of largest aperture on the top followed by sieves of gradually decreasing pore size)

method :- the powder whose particle size is to be determined is placed on the nest of sieves
↓
the powder is shaken for a definite time
↓
powder retained on sieves is collected and weighed
⇓

The data obtained is analysed and particle size and size distribution is calculated.

- This techniques generally used for coarse particles (more than 50 µm in size).

Advantage-

→ Sieving method is inexpensive and simple.

Disadvantage-

→ Particles below 50 µm difficult to measure.
→ Chances of attrition during sieving.
→ Need large amount of powder.

50 - 1500 µm

③ Sedimentation Method :- (Andreasen pipette)

(1 µm to 200 µm)

→ The apparatus consist of a 550 ml cylindrical vessel about 5.5 cm. internal diameter. (with scale graduated from 0-20 cm)

→ Stopper has 10 ml bulb pipette fitted with two way stopcock (side tube for draining sample)

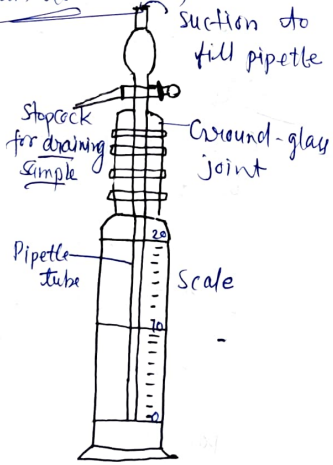


Fig. Andreasen pipette.

Method :-

1 or 2% suspension of the powder is prepared
↓
the suspension is introduced into vessel upto 550 ml mark
↓
vessel is stoppered and shaken
↓
pipette is then placed and vessel is kept undisturbed at a constant temp.
↓
at various intervals, 10 ml samples of suspension are withdrawn through two way stopcock
↓
placed in a previously weighed china dishes
↓
Samples are evaporated and weighed.

⇒ The particle diameter at various time periods is calculated by using Stoke's equation-

$$D_{st} = \frac{18\,\eta_0\,h}{(\rho_s - \rho_0)\,g\,t}$$

Where,

η_0 = viscosity of medium
h = distance of fall in time t sec
ρ_s = density of particle
ρ_0 = Density of dispersion medium.
g = Acceleration due to gravity.

Advantage-
→ Simple and inexpensive.
→ The result obtained are precise.

Disadvantage-
→ very small particles can not be determined.
→ Method is laborious → separate analysis for each sample.

④ Conductivity Method or Coulter Counter Method

- used for measuring particle volume.
- Range → 0.5 μm to 500 μm.

Principle:- When a particle suspended in a conducting liquid passed through a small orifice.
(on either side of which are electrodes)
↓
a change in electric resistance occures.

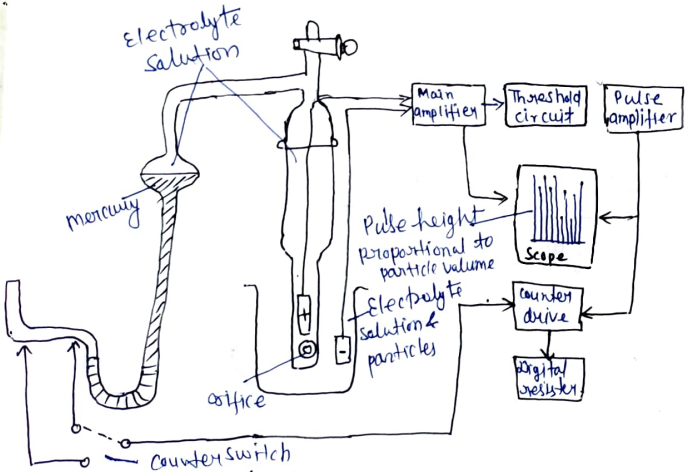


Fig- Coulter Counter Method.

⇒ A known volume of a dilute suspension is pumped through the orifice
(electrolyte located on either side of the apparatus)
↓
a constant voltage is applied through electrodes to produce a current
↓
the change in the electrical singnal that occurs when particles occupies the orifice and displaces its own volume of electrolyte.
↓
Change in resistance b/w electrodes cause voltage pulse which is amplified and proceesed electronically.

⇒ The magnitude of pulse is generated which is proportional to the volume of particles.

Advantage-
→ It is one of the precise and accurate method.
→ Analysis range is wide.

Disadvantage -
→ Aggregation of particles produce wrong result.
→ Coarse particle blocking orifice.

Particle Shape and Surface Area

- Particle shape affects the → packing properties
  → flow properties
  → Surface Area
- Surface area per unit weight or volume.
  ↓
  is an important characteristics which determines
  - Surface adsorption
  - dissolution rate.

Particle Shape:-

A ~~sher~~ sphere has a maximum surface area per unit volume
↓
more asymmetric the particle → the greater is surface area per unit volume.

⇒ A sphere is characterised by its diameter.

⇒ An asymmetric particle is more difficult to characterise in terms of surface diameter -
↓
So asymetric particles surface diameter is measured in terms of some equivalent spherical diameter.

Surface area of sphere = $S = \pi d^2$ ↳ diameter

volume of sphere $V = \frac{\pi d^3}{6}$.

⇒ So, to estimate surface area or volume of an asymmetric particle.
↳ It is necessary to choose a diameter that relates this to surface area or volume of a sphere through a correction factor.

⇒ Suppose → the particle size is determined microscopically
↓
the projected diameter is d_p.

So, Surface area $= \alpha_s d_p^2 = \pi d_s^2$.

where, α_s = surface area factor
d_s = equivalent surface diameter.

$$\text{Volume} = \alpha_v d_p^3 = \frac{\pi d_v^3}{6}$$

where, α_v = volume factor
d_v = equivalent volume diameter.

⇒ For a sphere,

$$\alpha_s = \frac{\pi d_s^2}{d_p^2} = 3.142$$

$$\alpha_v = \frac{\pi d_v^3}{6 d_p^3} = 0.524$$

⇒ The ratio α_s / α_v is used to characterise particle shape.
When particle is spherical $\alpha_s / \alpha_v = 6$

$$\frac{d_s}{d_v} = \frac{3.142}{0.524} = 6$$

⇒ If this ratio exceeds the maximum value of 6 → particle deviate from being spherical.

⇒ More this ratio exceeds from 6 → more asymmetic area the particles.

Specific Surface :-

⇒ The specific surface of a powder is defined as the surface area per unit volume (S_v) or per unit weight (S_w).

⇒ The specific surface area per unit volume is given by —

$$S_v = \frac{\text{surface area of particle}}{\text{volume of particles}}$$

$$S_v = \frac{k\alpha_s d^2}{k\alpha_v d^3} = \frac{\alpha_s}{\alpha_v d} \quad \text{—①}$$

where, d = volume - surface mean diameter

⇒ the surface area per unit weight is

$$S_w = S_v/\rho$$

where, ρ = true density of particles

⇒ Putting the value of S_v from equation ①

$$S_w = \frac{\alpha_s}{\rho\, d_{vs}\alpha_v}$$

for spherical or nearly spherical particles

$$S_w = \frac{6}{\rho\, d_{vs}}$$

(as $\alpha_s/\alpha_v = 6$ for a sphere)

Methods for determining Surface Area

⇒ The surface area of a powder can be determined indirectly from knowledge of → particle size distribution
↳ Volume determined by coulter-counter.

⇒ The surface area can directly determined by two methods —

① the ~~ads~~ adsorption method → By solute method / By Gas method
② The air permeability method.

① Adsorption Method :-

⇒ Particles with a large specific surface (small particle size) are good adsorbents of gases and solute from solution.

⇒ The amount of gas or solute adsorbed on powder sample to form a monolayer is found out and from this data surface area of the powder is determined.

ⓐ By using a solute which forms a monolayer :—

In this method, a solution of solute is prepared in a medium in which adsorbent powder is insoluble.

↓

a known amount of powder is then added and content was stirred for a sufficient time. (till equilibrium)

↓

the powder is filtered and amount of solute remaining in solution is determined (by suitable method).

⇒ the difference between quantity added and that remaining in the solution
↓
gives the quantity that has been adsorbed.

⇒ From this value → the amount adsorbed per gram of powder is calculated.

(b) By using adsorption of gas on powder –

Instrument is used is called Quantasarb.

- The powder whose surface area to be determined is introduced into a cell in the instrument and
↓
nitrogen which is the adsorbate gas and helium which is an inert gas (not absorbed).
passed through the powder in the cell

A thermal conductivity detector measure the amount of nitrogen adsorbed at every equilibrium pressure.
↓
a bell shaped curve is obtained

→ signal height gives rate of adsorption of nitrogen.
→ area under curve provides amount of gas adsorbed.

⇒ The volume of nitrogen gas V_m in cm^3 absorbed by 1 gram of powder (when monolayer formed)
↓
given by Brunauer, Emmett and Teller (BET) equation –

$$\frac{P}{V(P_0 - P)} = \frac{1}{V_m b} + \frac{(b-p)}{V_m b} \cdot \frac{P}{P_0}$$

Where,

V = Volume of gas in cm^3 adsorbed per gram of powder at pressure P.

P_0 = Saturated vapour pressure of liquified nitrogen at temp. of experiment.

b = Constant → gives the difference b/w → heat of adsorption & heat of liquifaction of nitrogen gas.

⇒ A plot of $\frac{P}{V(P_0 - P)}$ against $\frac{P}{P_0}$ → gives a straight line
↓
Slope – b
intercept – V_m.

⇒ The specific surface of the powder is obtained by –

$$S_w = \frac{A_m N}{m/\rho} \times V_m$$

Where,

m/ρ = molar volume of gas = 22,414 cm^3/mole

N = Avogadro's number 6.02×10^{23}

A_m = area of single close packed gas molecule adsorbed as a monolayer on surface of powder particles.
for nitrogen the value is 16.2×10^{-16} cm^2.

② Air Permeability Method :-

⇒ this method is based on the principle that

↓

the resistance offered to the flow of fluid (air) through a plug of compacted powder is proportional to the surface area of the powder.

⇒ The greater the surface area per gram of powder,
↳ the greater is the resistance to flow.

⇒ Instrument is called – Fisher - Subsieve sizer.

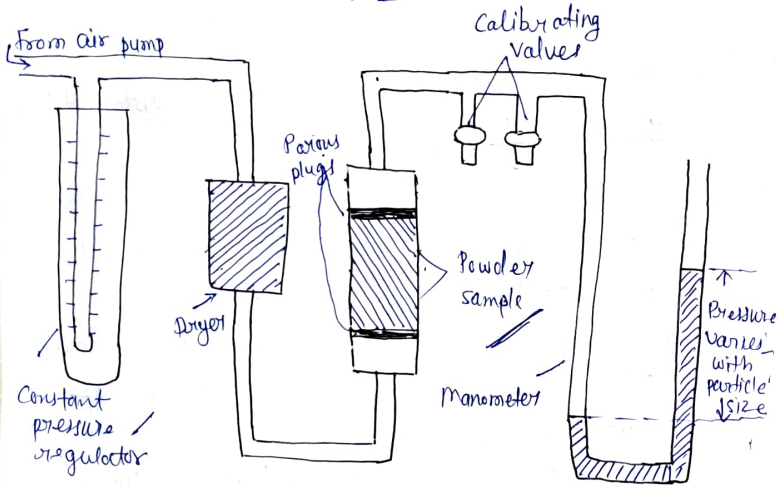


Fig. the fisher Subsieve sizer

⇒ A plug of powder → considered as a series of capillaries whose diameter related to average particle size

↓

internal surface area of capillary is a function of surface area of particles.

⇒ According to Poiseuille's equation –

$$V = \frac{\pi d^4 \Delta P t}{128 l \eta}$$

Where,

V = total volume of air flow
l = length
d = internal diameter
t = time
ΔP = Pressure difference
η = viscosity of fluid (air)

⇒ When air flow through plug of compacted powder

↓

resistance to flow of air occurs.

⇒ This resistance is related to surface area of the powder.

⇒ So as per Kozeny – Carman equation –
derived from Poiseuille's equation –

$$V = \frac{A}{\eta S_w^2} \propto \frac{\Delta P t}{kl} \times \frac{\varepsilon^3}{(1-\varepsilon)^2}$$

Where,

A = Cross sectional area of plug
K = Constant (usually 5.0 ± 0.5)
ε = porosity

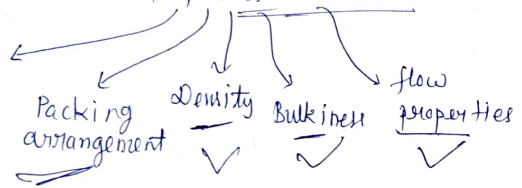
From this equation specific surface (Sw) can be calculated.

Derived Properties of Powders

Particle size distribution, surface area } two fundamental properties of powders

↓

from these a number of derived properties can be obtained



Porosity of Powders :-

- for a non-porous material → bulk volume = true volume
- most pharmaceutical solids are porous
  - ↓
  - they have internal pores or capillary space
  - ↓
  - so bulk volume > true volume
- ⇒ The volume of the spaces known as void volume (V)

$$V = V_b - V_p$$

Where,

V_b = bulk volume

V_p = True volume

- The porosity or voids (ε) is defined as
  - ↓
  - the ratio of the void volume to bulk volume of the powder packing.

$$\varepsilon = \frac{V_b - V_p}{V_b} = \frac{V_b}{V_b} - \frac{V_p}{V_b}$$

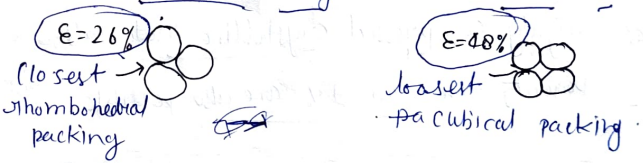
$$\boxed{\varepsilon = 1 - \frac{V_p}{V_b}} \qquad \boxed{\varepsilon = \frac{V_b - V_p}{V_b}}$$

⇒ Porosity is expressed as percentage. that is $\varepsilon \times 100$.

⇒ Packing Arrangements :-

⇒ Theoretically two types of packings are possible —

- closest → rhombohedral packing
- Loosest → cubical packing



⇒ The fraction of the total volume occupied by free space between the particles is the porosity.

⇒ If the particles are spherical in powder bed

↓

theoretical porosity

26% is possible in closest packing and

48% in loosest packing.

⇒ However in actual situations

↓

pharmaceutical powders have porosities ranging from 30 – 50 %.

⇒ In some cases → when particles of varying size are present
↓
porosity lower than theoretical minimum of 26% is also possible.
This is because small particles fit in the void spaces → so giving a reduced porosity.

⇒ on other hand → if powder contains floccules or aggregates
↓
porosity may go beyond theoretical maximum of 40%.
– due to large void spaces with entrapped air.

⇒ In case of highly compressed crystalline materials
↓
porosity less than 1% are also possible.

Flow Properties of Powders

⇒ It is important parameter to be considered in the production of pharmaceutical dosage forms.

⇒ Most of the processes such as → uniform filling of dies during tabletting
filling of capsules
↓
directly depend on flow properties of powder mass.

⇒ other processes like → gravity feeding of powders
↳ pneumatic and hydraulic tranfer
↓
also depends on flow properties.

⇒ Poor flow is powders in generally due to –

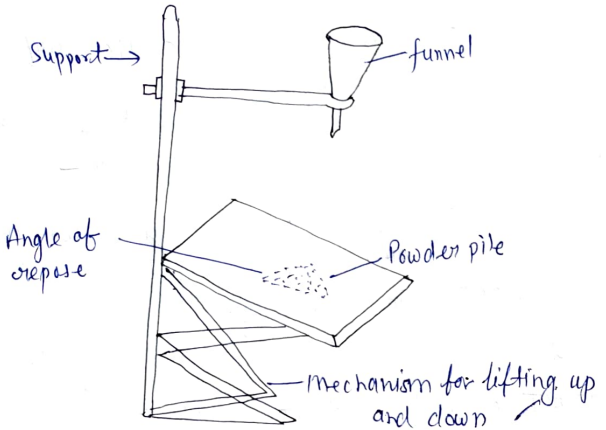
① Cohesiveness or stickiness b/w particles due to presence of Van der walls, surface tension and electrostatic forces.
② Adhesion b/w particles and the container wall.
③ Friction between particles due to surface roughness.
④ Physical interlocking of particles due to irregular shape.

Assessment of flow properties of Powders:-

⇒ Flow properties of powder generally assessed by
↓
angle of repose of powders.

⇒ It is defined as
↓
the maximum angle possible b/w the surface of a pile of powder and horizontal plane.

⇒ the angle of repose is determined by
↓
allowing a mass of powder to flow freely through an orifice from a certain height and form a conical heap on horizontal surface.



⇒ As the heap is formed → the particles slip and roll over each other until particles just balance the gravitational force.

⇒ The angle which the heap forms with horizontal surface is the angle of repose and is determined by,

$$\tan\theta = h/r$$

Where,
- θ = angle of repose
- h = hight of heap of powder
- r = radius of base of heap of powder

Angle of repose (θ) degrees — Flow properties –
- < 25 → Excellent
- 25–30 → Good
- 30–40 → satisfactory
- 40–50 → Poor
- > 50 → very poor

Compressibility Index and Hausner Ratio–

Carr's Index :-

$$\text{Compressibility Index}(\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner Ratio –

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Carr's Index	Flow character	Hausner's Ratio
≤ 10	Excellent	1.0 – 1.11
11–15	Good	1.12 – 1.18
16–20	fair	1.19 – 1.25
21–25	slightly poor	1.26 – 1.34
26–31	Poor	1.35 – 1.45
32–37	very poor	1.46 – 1.59
>38	Extremely poor	>1.60

Improvement of flow properties –

① Altering the Particle Size –

Increasing the averages particle size → improves the flow properties due to reduction in cohesive force.

② Removal or Addition of fines –

Presence of small particles improve flow properties by filling up in pits and crevices of particle surface.

② Larger proportion of fines → retard flow properties.
So optimum concentration of fines is desirable.

③ Altering the particle shape and texture –
Spherical particles move better (flowability) than irregular particles.

④ Altering the surface ~~Area~~ forces:
Reduction of electrostatic charges on particles
↓
improve flow ~~pro~~ properties.

⑤ Removing Extra moisture –
Removal of moisture → improve flow properties (by decreasing cohesiveness).

⑥ ~~Addition~~ Adding flow activators or Glidants
Flow properties of pharmaceutical powders may be improved by addi

Bulkiness

⇒ The reciprocal of bulk density is known as bulk or bulkiness or specific bulk volume.

⇒ Bulkiness usually increases with decrease in particle size.

⇒ It is a useful property → while choosing a suitable container for bulk powders
↘ during filling of capsules.

Densities

Density is defined as weight per unit volume.

Types of density –

W/V

① Bulk Density –
It is defined mathematically as:

$$\text{Bulk density } (\rho_b) = \frac{\text{mass of a powder (w)}}{\text{bulk volum } (V_b)}$$

② Granule density
Granule density is determined for the granules that are employed in the manufacture of tablet.
Granule density is defined as:

$$\text{Granule density } (\rho_g) = \frac{\text{granule weight (w)}}{\text{granule volum } (V_g)}$$

* Granule volume can be measured by mercury displacement method.

③ True density –
It is the density of the material itself.
It is defined as:

$$\text{True density } (\rho_p) = \frac{\text{weight of powder (w)}}{\text{true volume of powder (v)}}$$